Herbs' Disease-matched Pharmacological Mechanisms of HuanglianJiedu Decoction in Behavioral and Psychological Symptoms of Dementia in Alzheimer's Disease

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Research Article

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Abstract

Along with cognitive deficit, behavioral and psychological symptoms in dementia (BPSD) is another characteration of Alzheimer's disease that hamper clinical management and exacerbate burden for caregivers. However, therapeutic management of BPSD remains challenging. HuanglianJiedu decoction (HLJDD), a traditional Chinese prescription which contains *Coptidis rhizome*(Huang lian), *Scutellariae radix* (Huang-qin), *Phellodendri chinrnsis cortex* (Huang-bai) and Gardeniae fructus (Zhi-zi), is applied to treat BPSD. So elucidating the herbs' disease-matched pharmacological mechanisms underlying HLJDD, further put forward each herbs' disease-matched combination are critical to the application of HLJDD. In this study, network pharmacology was used to determine the targets and biological processes regulated by HLJDD in the treatment of BPSD. Moreover, molecular docking was utilized to evaluate the binding activity between the herbs' main active ingredients and neurotransmitter receptors. The results showed that the KEGG signaling pathway of HLJDD in treating BPSD mainly lies in TNF signaling pathway and AGE-RAGE signaling pathway in diabetic complications. *Scutellariae radix* and *Phellodendri chinrnsis cortex* exhibited better anti-BPSD effects when compared to *Coptidis rhizoma* and *Gardeniae fructus*. *Scutellariae radi*x exhibited superior anti-neuroinflammation functions, with better blood vessel regulation effects. *Phellodendri chinrnsis cortex* showed a higher binding affinity to the dopamine D2 receptor (DRD2) and 5-hydroxytryptamine receptor 2A (HTR2A). *Coptidis rhizoma* and *Gardeniae fructus* were better in neuronal signaling. In conclusion, for treating BPSD, *Scutellariae radix* and *Phellodendri chinrnsis cortex* are the principal herbs while *Coptidis rhizoma* and *Gardeniae fructus* are the ancillary herbs. Beta-sitosterol, stigmasterol, chelerythrine, campesterol and berberine are the potential effective ingredients in treating BPSD.

Introduction

More than 90% of AD patients who suffer from BPSD which including anxiety, agitation, aggression, irritation, depression, *etc.*, have no effective treatment yet(Eissa et al., 2020). Molecules involved in the pathogenesis of BPSD which are essential to the treatment of BPSD have been studied by many researchers. Neuroinflammation, a response that involves neurons and microglia, has been reported to characterize several neurodegenerative diseases and neuropsychiatric conditions, resulting in the elevated production of pro-inflammatory cytokines, such as IL-6, TNF-α, IL-8, and IL-4. Notably, microglia activation is the first sign of neuroinflammation. Activated microglia can release various oxidants such as reactive oxygen species and activate several genes and proteins, such as inducible nitric oxide synthase(Tang et al., 2017). Neurotransmitters and their receptors are also considered to play a crucial role in BPSD(Lopez-Leon et al., 2008). APOE epsilon4, the most common genetic risk factor for the late-onset of AD, elevates the risk of BPSD(Lin and Lane, 2019). Those molecular mechanism are confirmed with the GeneCards databases in this research, which were utilized to identify the potential targets of BPSD. And the evaluation of molecular mechanisms provides a powerful approach for pharmacotherapy for BPSD. While until now, the efficacy of anti-psychotics for the treatment of BPSD is scanty. Anti-psychotic drugs used in the clinical management of BPSD. have extrapyramidal severe side effects (EPS)(Marcinkowska et al., 2020). The current primary therapeutic option for AD, acetylcholinesterase inhibitors, is debatable for treating BPSD(Seibert et al., 2021). Memantine, an NMDA receptor antagonist for treating moderate-to-severe AD, inhibits antipsychotic-induced EPS, but is controversial for treating BPSD (Ma et al., 2019). In this research, memantine is selected as an active control medicine since memantine has been one candidate medication for treating BPSD(Youn et al., 2021). Now several researchers turn their attention to natural herbs as an alternative or complementary method to BPSD for their clinical efficacy with minimal side effects.

Traditional Chinese medicine (TCM) plays an important role in medical diagnosis and treatments. Based on the TCM theory, Chinese formulas contain a mixture of herbs, combined based on the following combination principle: "monarch (Jun), minister (Chen), assistant (Zuo), and guide (Shi)" meaning that herbs play primary, secondary, auxiliary, or harmonic roles, respectively(Guo et al., 2018). Herbs' disease-matched pharmacological mechanisms will help people to understand herbs' combination and providing herbs' disease-match combination which are good for the application of TCM. BPSD has different TCM syndrome differentiation. "Toxin damaging brain collateral", an essential BPSD differentiation, was proposed by Yongyan Wang, means brain collateral is injured by fire toxins(Ning, Y.Z. et al., 2019; Zhou, L. et al., 2012). And purging fire for removing toxins is commonly used as the treatment method. HLJDD, a classic prescription for heat-clearance and detoxification, is frequently used in BPSD(Stelzer et al., 2016). In HLJDD, *Coptidis rhizoma* plays the monarch role, *Scutellariae radix* plays the minister role while *Phellodendri chinrnsis cortex* and *Gardeniae fructus* play the assistant and guide roles, respectively(Qi et al., 2019). But for specific disease, this combination maybe not suitable. To elucidate HLJDD's disease-matched mechanism and combination in treating BPSD, we utilized network pharmacology and molecular docking to provide prior herbs for BPSD therapeutics by emphasizing on their molecular activities. In this research, we analyzed the KEGG signaling pathway under HLJDD in treating BPSD, and each herbs' disease-matched mechanisms. We not only put forward the prior herbs of HLJDD for BPSD, but also emphasized the potential ingredients to treat BPSD. The chart flow of this research was followed bellowed (Figure 1).

Materials And Methods

Determination of active ingredients and their matched potential target proteins

A natural plant contains various chemical compounds. We used the TCM systems pharmacology database and analysis platform (TCMSP, https://tcmspw.com/index.php) to determine the main active ingredients in the herbs. Compounds were filtered by oral bioavailability (OB) ≥ 30%, drug-likeness (DL) ≥ 0.18, and drug half-life (HL) ≥ 4 h. The potential molecular targets for the active compounds were predicted using the search tool for interactions of chemicals database (STITCH, http://stitch.embl.de/), with the species limited to "Homo sapiens."

Potential targets prediction for BPSD

BPSD-associated protein targets were identified using the GeneCards database (http://www.genecards.org/) (Shannon et al., 2003). These target proteins exhibited a higher rank score, and a higher correlation with BPSD. The keywords used in the search were "behavioral and psychological symptoms of dementia in Alzheimer's disease." The top 50% of the predicted targets were selected as potential BPSD targets.

Network construction and analysis

We constructed the "compounds-targets-BPSD" networks by Cytoscape 3.7.2 software(Bindea et al., 2009). The .csv format files whose data combined target compounds and BPSD targets were imported into Cytoscape. The node size was based on the target proteins score values as provided by the GeneCards database. Cross-targets between active compounds and BPSD were the herbs' putative key targets, and set with a red rectangle node. Memantine was used to identify the potential neurotransmitter receptors.

Enrichment analysis of target proteins

We performed Gene Ontology (GO) functional enrichment analysis using the ClueGO plugin(Wang et al., 2021), with the species limited to "Homo sapiens" and $p < 0.05$.

Molecular docking for active compounds with DRD2 and HTR2A

Memantine was selected as the active control medicine. The molecular mechanism of memantine on BPSD was determined by network pharmacology, same as the HLJDD herbs. The results showed that DRD2 and HTR2A were the targets of neurotransmitter receptors. Then molecular docking studies were conducted using AutoDock software(Wang et al., 2021) to evaluate the affinity of the active compounds bind with DRD2 and HTR2A neurotransmitter receptors. Crystal structures of the proteins were downloaded from the RCSB Protein Data Bank (http://www.rcsb.org/). PDB ID “6CM4” and “6A93”, whose ligand is Risperdal, were selected as DRD2 and HTR2A’s crystal structure. Memantine, Risperdal, and HLJDD’s active compounds were then docked with DRD2 and HTR2A.

Results

HLJDD’s main active compounds and potential target proteins

After searching the TCMSP database, we identified 80 compounds in HLJDD. Scutellariae radix, Coptidis rhizoma, Phellodendri chinrnsis cortex, and Gardeniae fructus have 32, 10, 27, and 11 ingredients, respectively. Then, these compounds were imported into the STITCH database to achieve the potential target proteins (Table 1).

TABLE 1: HLJDD’s active compounds and potential molecular target proteins

Herbs	Active ingredients	Potential target proteins
Scutellariae radix	acacetin	IL13，CYP1A2，VEGFA，JUN，STAT1，NR1I2，SELE，CYP1A1，IL5，CYP1B1
Scutellariae radix	wogonin	MMP9，MYC，HMGB1，MCL1，PTGS2，CDK9，GATA1，KCNK10，PLSCR1，CCL2
Scutellariae radix	baicalein	MAPK1，ALOX15，CDK4，MMP2，PLAU，CYP1A2，AKT1，CYP3A4，ALOX12，MMP9
Scutellariae radix	oroxylin a	MAPK3，BDNF，HK2，SIRT3，CASP8，PPIF，IL6，SOD2，PARP1，NOS1
Scutellariae radix	Panicolin，skullcapflavone I，	CASP3
Scutellariae radix	beta-sitosterol	DHCR24，CASP3，ABCG5，SREBF2，ICAM1，ABCG8，CYP7A1，SREBF1，APOE，ABCB11
Scutellariae radix	Stigmasterol	TNF，IL8，ABCA1，ABCG8，NR1H2，SREBF2，ABCG5，NR1H3，IL10，SLCO1B1
Scutellariae radix	coptisine	PAWR，XPO1，TNFSF11，ESF1
Coptidis Rhizoma	quercetin	MCL1，ATP5B，CYP1A1，HIBCH，HCK，STK17B，SLC2A2，CYP1B1，CYP2C8，PIM1
Coptidis Rhizoma	berberine	CCND1，CASP3，DPP4，TP53，AKT1，MAPK1，HMOX1，LDLR，PCSK9，ATP5G2
Coptidis Rhizoma	coptisine	PAWR，TNFSF11，ESF1，XPO1
Phellodendri chinrnsis cortex	berberine	PCSK9，ATP5G2，HMOX1，MAPK1，TP53，CASP3，AKT1，DPP4，LDLR，CCND1
Phellodendri chinrnsis cortex	coptisine	PAWR，XPO1，ESF1，TNFSF11
Phellodendri chinrnsis cortex	rutaecarpine	CYP1A1，TNF，CYP1A2
Phellodendri chinrnsis cortex	Chelerythrine	GAPDH，PRKCE，PLA2G1B，F2，CFTR，CHI3L2，SELP，PLA2G2A，CORT，ABCB11
Phellodendri chinrnsis cortex	Stigmasterol	IL10，TNF，SREBF2，IL8，SLCO1B1，ABCG8，ABCG5，NR1H2，NR1H3，ABCA1
Phellodendri chinrnsis cortex	beta-sitosterol	ABCG5，SREBF2，DHCR24，CYP7A1，ABCB11，CASP3，ICAM1，SREBF1，ABCG8，APOE
Phellodendri chinrnsis cortex	Fumarine，protopine，	HRH1，F2，KIAA0101
Phellodendri chinrnsis cortex	quercetin	CYP1B1，STK17B，PIM1，SLC2A2，CYP1A1，HCK，ATP5B，HIBCH，CYP2C8，MCL1
Phellodendri chinrnsis cortex	poriferast-5-en-3beta-ol ，beta-sitosterol，	CASP9，NR1H2，PARP1，CASP3，ABCG8，ABCG5，ICAM1
Phellodendri chinrnsis cortex	campesterol	HSD3B2，ABCG8，ABCG5，CYP7A1，DHCR24，CSN1S1，NR1H2
Gardeniae fructus	Sudan III	CELA1，CELA3B
Gardeniae fructus	quercetin	CYP1B1，SLC2A2，STK17B，CYP2C8，HCK，CYP1A1，MCL1，PIM1，HIBCH，ATP5B，ATP5F1B
Gardeniae fructus	beta-sitosterol	SREBF1，CYP7A1，ABCB11，CASP3，ABCG5，APOE，ABCG8，SREBF2，DHCR24，ICAM1
Gardeniae fructus	kaempferol	UGT1A9，UGT1A8，UGT3A1，UGT1A7，CYP1B1，CDK1，AHR，UGT1A3，NR1I2，RPS6KA3
Gardeniae fructus	Stigmasterol	ABCG8，IL8，TNF，NR1H2，NR1H3，SREBF2，SLCO1B1，ABCG5，ABCA1，IL10

“Compounds-targets-BPSD” network and GO biological process analysis

In this network, the red rectangular nodes represent the cross-targets (key targets) between herbs and BPSD. The targets for *Scutellariae radix* were the highest (24 key targets), followed by *Phellodendri chinrnsis cortex* (15 key targets). *Coptidis rhizoma* and *Gardeniae fructus* have 7 and 5 key targets respectively. Referring to key targets number, *Scutellariae radix* and *Phellodendri chinrnsis cortex maybe* better than *Coptidis rhizoma* or *Gardeniae fructus* in treating BPSD (Table 2).

TABLE 2: Cross-targets (key targets) between herbs and BPSD and biological functions of key targets

Herbs	Cross-targets between herbs and BPSD (BPSD correlation score)	Number of cross-targets	Biological functions of cross-targets	Number of biological functions
Scutellariae radix	APOE (156.68), TNF (114.77), SOD2 (114.23), IL 6 (105.12), BDNF (104.54), IL 10 (86.21), VEGFA (72.66), AKT1 (66.45), CCL2 (66.37), MAPK1 (52.1), PLAU (41.02), CASP3 (37.17), ICAM1 (37.08), PTGS2 (35.32), NOS1 (32.33), MMP9 (30.39), MYC (30.15), IL 13 (29.05), MAPK 3 (26.17), HMGB 1 (23.14), JUN (22.83), STAT1 (20.14), TNFSF 11 (18.98), CYP3A4 (17.31)	24	positive regulation of smooth muscle cell proliferation; lipopolysaccharide-mediated signaling pathway; regulation of neuroinflammatory response; regulation of nitric oxide biosynthetic process; positive regulation of endothelial cell proliferation; regulation of smooth muscle cell proliferation; positive regulation of nucleotide biosynthetic process; positive chemotaxis; negative regulation of epithelial cell differentiation; regulation of endothelial cell proliferation; negative regulation of cysteine-type endopeptidase activity involved in apoptotic process; positive regulation of blood vessel endothelial cell migration; cellular response to interleukin-6; Vasodilation; regulation of DNA-templated transcription, initiation; regulation of interferon-alpha production;	16
Phellodendri chinrnsis cortex	APOE (156.68), TNF (114.77), IL 10 (86.21), TP 53 (72.85), AKT 1 (66.45), MAPK 1 (52.1), HMOX 1 (50.08), LDLR (40.09), F 2 (38.83), CASP 3 (37.17), ICAM 1 (37.08), PLA2G2A (33.98), CFTR (21.04), CASP 9 (20.76), TNFSF 11 (18.98), SELP (17.65)	15	response to nicotine; glial cell apoptotic process; plasma lipoprotein particle clearance; regulation of platelet activation; positive regulation of anion transport	5
Coptidis	TP53 (72.85), AKT 1 (66.45), HMOX 1 (50.08), LDLR (40.09),	7	cellular response	3

rhizoma	MAPK 1 (52.1), CASP 3 (37.17). TNFSF 11 (18.98)		to cadmium ion; response to nicotine; negative regulation of macroautophagy
Gardeniae fructus	APOE (156.68), TNF (114.77), IL 10 (86.21), CASP 3 (37.17), ICAM 1 (37.08)	5	regulation of amyloid-beta formation; regulation of membrane protein ectodomain proteolysis; regulation of nitric oxide biosynthetic process
		3	

We used the GO biological process analysis to study the biological functions of the key protein targets. The KEGG signaling pathway of HLJDD which mainly involved in AGE-RAGE signaling pathway in diabetic complications, TNF signaling pathway, and Bile secretion were showed in figure 2. For each herb's analyzation, the results showed in figure 3-6. *Scutellariae radix* involves in the most biological function processes. Mainly lies in positive regulation of smooth muscle cell proliferation, lipopolysaccharide-mediated signaling pathway, regulation of neuroinflammatory response, and regulation of nitric oxide biosynthetic process (Figure 3). Smooth muscle cell proliferation, especially vascular smooth muscle cells, are essential during cell growth or injury(Sweeney et al., 2018). Blood vessels with vascular smooth muscle cells play an important role in normal brain functions. Apart from supplying adequate blood, they help maintain its structural integrity and function. Shortages in cerebral blood flow and blood-brain barrier dysfunction are early findings in neurodegenerative disorders. Cerebral blood flow shortage, impaired cerebrovascular reactivity, and impaired hemodynamic responses are increasingly prevalent in the early stages of AD(Zhou et al., 2020). Nitric oxide (NO) is a small free radical molecule with an endothelium-derived relaxing factor. Adequate levels of NO in the vascular endothelium are critical for regulating blood flow and vasodilation. Moreover, NO plays a vital neuronal signaling role(Tejero et al., 2019). The lipopolysaccharide, a gram-negative bacterial endotoxin released from the cell wall, mediates inflammation in the body, involving in regulating the expression of potential inflammatory factors(Guo et al., 2018). Studies have linked schizophrenia with neuroinflammatory conditions and microglia, which have been correlated to the pathogenesis of schizophrenia. Neuroinflammatory changes observed in schizophrenia involve abnormal astrocyte functions(Gomes et al., 2015). For biological function processes, *Scutellariae radix* are better than the others in treating BPSD.

Phellodendri chinrnsis cortex involved in 5 biological function processes. They were the response to nicotine, glial cell apoptotic process, plasma lipoprotein particle clearance, regulation of platelet activation, and positive regulation of anion transport (Figure 4). Microglia, the resident innate immune cells in the brain, are important in AD immune responses. They act as sentinel and protective cells, but may become inappropriately reactive in AD to drive neuropathology(Wen and Klionsky, 2016). With advances in age, microglia exhibit enhanced sensitivity to inflammatory stimuli, similar to that observed in brains with ongoing neurodegeneration(Chen et al., 2017). Platelets, critical blood flow factors, are anucleate blood cells whose principal function is to stop bleeding by forming aggregates for hemostatic reactions. Platelet aggregates are also involved in pathological thrombosis and play an essential role in inflammation(Forcella et al., 2020). Studies have documented that Nicotine might be involved in the pathophysiology of psychosis. Smoking is correlated with depression. In animal models, Nicotine exhibited anxiolytic properties. Depressed people are more likely to smoke and more likely to develop severe

depressive episodes upon smoking cessation. Nicotine has also been observed to exhibit similar cognitive improvements in AD patients(Wen and Klionsky, 2016). However, the relationship between smoking and AD has not been clearly elucidated(Chen et al., 2017).

Coptidis rhizoma and *Gardeniae fructus* each have three biological function processes. *Coptidis rhizoma* involved in cellular response to cadmium ion, response to nicotine, and negative regulation of macroautophagy (Figure 5). Cadmium, a metal that resembles zinc and calcium, is also crucial for neuronal signaling. Cadmium exposure is associated with neurodegenerative diseases such as AD. It can alter neurotransmitters' release, cause oxidative stress, damage the mitochondria, and induce apoptosis(Bucki et al., 2020). Macroautophagy is an evolutionarily conserved dynamic pathway that functions primarily in a degradative manner. Various diseases are associated with macroautophagic dysregulation. Macroautophagy plays a critical role in cellular homeostasis. Insufficient or excessive macroautophagy can seriously compromise cell physiology(O'Boyle et al., 2011). *Coptidis rhizoma* was shown to negatively regulate macroautophagy while *Phellodendri chinrnsis cortex* regulated glial cell apoptosis. *Gardeniae fructus* involved in regulation of amyloid-beta formation, regulation of membrane protein ectodomain proteolysis, and regulation of nitric oxide biosynthetic process (Figure 6). In AD, the abnormal accumulation of amyloid-β released from amyloid precursor protein and neuroinflammation are its partially pathologic hallmarks. Amyloid-β accumulation also causes indirect injuries to neurons by inducing neuroinflammation(Forcella et al., 2020).

“Compounds-targets-BPSD” network of memantine

Patients with moderate to severe AD exhibit relatively severe cognitive and psychological symptoms. N-Methyl-D-aspartic acid (NMDA) is one of the main therapeutic options. Memantine is the most common therapeutic choice for NMDA(Zhang et al., 2013), was a choice to treat BPSD. In our study, memantine was used as the reference drug. We established the “compounds-targets-BPSD” network of memantine to determine its potential neurotransmitter receptor mechanism in BPSD. It was found that DRD2 and HTR2A were the neurotransmitter receptors associated with BPSD.

Results of molecular docking

Serotonin and its receptors, particularly the HTR2A, play roles in cognitive behaviors and psychiatric conditions such as depression, schizophrenia, and AD(Lopez-Leon et al., 2008). A multitarget-directed ligand, acting on HTR2A and DRD2, has been shown to exert an anti-aggressive and antipsychotic activity and is, therefore, a promising therapeutic option for BPSD(Paterson and Nordberg, 2000). In this study, herbs active ingredients were docked with DRD2 and HTR2A. The 3D structures of the active ingredients were downloaded from the TCMSP database in .mol2 format. They were later converted into .pdb format using the Open Babel GUI software(Teaktong et al., 2004). The local search parameters and rigid file names of the macro molecule models were used when docking. The software's default values were set as our docking parameters. Grid box sizes were: DRD2: x-dimension: 62, y-dimension: 84, z-dimension: 126, spacing: 0.375, X center: 17.469, y center: 7.307, z center: 2.7. HTR2A: x-dimension: 126, y-dimension: 62, z-dimension: 84, spacing: 0.497, X center: 30.895, y center: 0.518, z center: 63.697. These parameters were minimally adjusted during docking.

The smaller of docking score, the lower of energy would be required, which means the binding between the compounds and the targets are stronger(Chen et al., 2020). We found that beta-sitosterol exhibited the lowest docking energy with DRD2 (-9.58 Kcal/mol) and HTR2A (-8.2 Kcal/mol) when compared to the other compounds, including memantine and Risperdal. Stigmasterol, chelerythrine, and campesterol also exhibited a lower docking

energy than memantine and Risperdal. *Phellodendri chinrnsis cortex* was shown to contain most of these good-docked compounds indicate that it's better than the other herbs in treating BPSD. (Table 3 and Figure 6).

TABLE 3: The docking results of the active ingredients with DRD2 and HTR2A

Name	DRD2 (PDB ID:6CM4) binding energy (Kcal/mol)	HTR2A (PDB ID:6A93) binding energy (Kcal/mol)	Herbs that contain this compound
memantine	-6.72	-6.02	
Risperdal	-7.71	-7.9	
beta-sitosterol	-9.58	-8.2	*Phellodendri chinrnsis cortex*, *Scutellariae radix*, *Gardeniae fructus*
stigmasterol	-9.17	-8.9	*Phellodendri chinrnsis cortex*, *Scutellariae radix*, *Gardeniae fructus*
chelerythrine	-8.1	-8.12	*Phellodendri chinrnsis cortex*
campesterol	-7.37	-8.67	*Phellodendri chinrnsis cortex*
berberine	-7.87	-7.61	*Phellodendri chinrnsis cortex*, *Coptidis Rhizoma*
Oroxylin a	-7.38	-6.42	
acacetin	-7.31	-5.8	
Sudan III	-6.87	-6.95	
baicalein	-6.7	-6.0	
kaempferol	-6.33	-5.49	
wogonin	-5.68	-5.95	
quercetin	-5.82	-5.04	
panicllin	-5.53	-5.74	
coptisine	-	-	
rutaecarpine	-	-	
fumarine	-	-	

Note: "-" indicates that the result has not been calculated. Red font color: means have lower binding affinity with DRD2 and HTR2A than memantine and/or Risperdal. Blue font color: means this herbs contain more good-dock compounds.

Discussion

HLJDD which contains four herbs *Coptidis rhizoma*, *Scutellariae radix*, *Phellodendri chinrnsis cortex*, and *Gardeniae Fructus* in a ratio of 3:2:2:3 shows the ability to dispel the heat and poison and relieve the associated syndromes. Qi Y's study showed that HLJDD may have the same efficacy as aripiprazole (antipsychotics) in treating AD without any significant adverse reaction(Qi et al., 2019). In this study, we utilized network pharmacology which is a novel tool for drug discovery to providing mechanism of HLJDD in treating BPSD. The results showed that TNF signaling pathway and AGE-RAGE signaling pathway in diabetic complications were the mainly signaling pathway of HLJDD involving in BPSD. Pro-inflammatory cytokines play an essential role in the

mechanism of depression in AD. In particular, TNF, a cytokine ligand, that participates in systemic inflammation, is increased during depression and cognitive impairment(Cassano et al., 2019). Besides, both TNF and its type 1 receptor (TNFRI) can regulate amyloid formation through secreted enzymes(Gao et al., 2021). The AGE-RAGE signaling pathway, when activated, can induce the production of NF-Kβ and inflammatory factors which are important mechanism of BPSD(Ye et al., 2021).

Though we recognized HLJDD can treat BPSD, but we confused if *Coptidis rhizome* and *Gardeniae Fructus* could have the higher proportion than *Scutellariae radix* and *Phellodendri chinrnsis cortex* when treating BPSD. So, following our research is herbs' disease-matched combination of HLJDD in treating BPSD. The combination of herbs into a prescription to enhance their overall therapeutic effects or eliminate the adverse effects(Tian et al., 2019), is referred to as TCM combination. Although prescriptions have conventional combinations, it is essential to consider novel combinations for different diseases. In this study, we propose an innovative method that is based on molecular mechanism for determining herbs combination. We investigated the novel combination of HLJDD in BPSD and the potential ingredients to treat BPSD. Our results showed that *Scutellariae radix* and *Phellodendri chinrnsis cortex* have better effectivity than *Coptidis rhizome* and *Gardeniae Fructus* in treating BPSD by technology of network pharmacology and molecular docking.

Scutellariae radix, the dry root of *Scutellariae baicalensis Georgi*, has been used as a traditional herbal preparation for the treatment of neuropsychiatric disorders(Li et al., 2013). Study showed that *Scutellariae radix* has been shown to ameliorate memory deficits and displays neuroprotective effects(Yun and Jung, 2014). *Scutellariae radix* may primarily targets alterations of the DA system, which are implicated in various neurological and mental disorders, and also in their comorbidity(Limanaqi et al., 2020). Tarrago's study showed that *Scutellariae radix* has the ability to inhibit prolyl oligopeptidase's activity which associated with schizophrenia, bipolar affective disorder, and related neuropsychiatric disorders(Tarrago et al., 2008). In this study, the results showed that *Scutellariae radix* can regulate the neuroinflammatory response, indicating a protect role of depression which is one of the BPSD symptoms.

Phellodendri chinrnsis cortex which is commonly used to remove damp heat, quench fire, and counteract toxicity, has been reported to possess neuroprotective activities(Jiang et al., 2017). Berberine, the major active ingredient of *Phellodendri chinrnsis cortex*, had been reported to possess the potential neuroprotective effect against mental depression, schizophrenia, cerebral ischemia, anxiety, and AD(Xian et al., 2013). Study reported that berberine has a protective effect on central nervous system disorders, such as Alzheimer's disease, mental depression, schizophrenia, and anxiety (Fan et al., 2019). In this study, the molecular docking results showed that *Phellodendri chinrnsis cortex* has better anti- psychosis effect through serotoninergic and dopaminergic systems.

It has been documented that serotoninergic, dopaminergic, and cholinergic systems are involved in BPSD pathogenesis, and the roles of HTR2A and DRD2 as therapeutic targets are evident(Paterson and Nordberg, 2000). We used molecular docking to determine the potential active ingredients that exhibited good binding activities to DRD2 and HTR2A. The best-docked compound was beta-sitosterol. The free binding energy of beta-sitosterol with DRD2 and HTR2A was -9.58 kcal/mol, -8.2 kcal/mol, respectively. Stigmasterol, chelerythrine, campesterol and berberine also exhibit good binding activities. They are the potential effective ingredients in treating BPSD which may give reference for the drug development and investigation insight.

The TCM theory verifies our results. Triple energizers in TCM theory mean upper, middle, and lower energizers. They are the birth and channel to run for Qi, blood, thin, thick fluids, and essence. Moreover, they also contact five Zang-

organs and six Fu-organs. *Scutellariae radix* affects the upper energizer, which consists of the brain and heart; *Phellodendri chinrnsis cortex* affects the lower energizer, which is the kidney and liver while *Coptidis rhizoma* influences the middle energizer that consists of the spleen and stomach. Kidney essence deficiency is a primary syndrome differentiation of AD in TCM theory. Due to the imbalance between yin and yang of liver functions, "Liver fire" is the largest contributor to BPSD(Shi et al., 2020). *Phellodendri chinrnsis cortex* acts on the lower energizer to purge the liver fire. "Su Wen" put forward that "the mind is the monarch's official, and the gods come out of it." In the compendium of Materia Medica, Shizhen Li of the Ming Dynasty proposed that "the brain is the house of primordial God." *Scutellariae radix* works on the heart and brain, belonging to the upper energizer. In conclusion, based on the TCM theory, *Scutellariae radix* and *Phellodendri chinrnsis cortex* are HLJDD's primary herbs.

Conclusions

The therapeutic value of natural products in the management of BPSD has increased due to their clinical efficacy and insignificant side effects. Different types of compounds have been reviewed for their biological activities. Our results showed that *Scutellariae radix* has more molecular targets and biological processes involved in BPSD while *Phellodendri chinrnsis cortex* exhibited more well-docked compounds: poriferast-5-en-3beta-ol (beta-sitosterol), Stigmasterol, chelerythrine, and campesterol, which have a lower affinity for DRD2 and HTR2A. *Scutellariae radix* and *Phellodendri chinrnsis cortex* were found to have the primary compounds for treating BPSD. *Scutellariae radix* plays an anti-inflammatory role while *Phellodendri chinrnsis cortex* regulates apoptotic processes and response to nicotine. They both regulate blood vessels. *Coptidis rhizoma* and *Gardeniae fructus* play the assistant role in BPSD, and are involved in neuronal signaling. Beta-sitosterol, stigmasterol, chelerythrine, campesterol and berberine are potential effective ingredients in treating BPSD.

Abbreviations

AD: Alzheimer's disease; BPSD: Behavioral and psychological symptoms in dementia; HLJDD: HuanglianJiedu decoction; DRD2: Dopamine D2 receptor; HTR2A: 5-hydroxytryptamine receptor 2A; TCM: traditional Chinese medicine; EPS: extrapyramidal severe side effects; TCMSP: TCM systems pharmacology database and analysis platform; OB: oral bioavailability; DL: drug-likeness; HL: half-life; STITCH: search tool for interactions of chemicals database; GO: Gene Ontology; D-CS: BPSD correlation score; NMDA: N-Methyl-D-aspartic acid; LPS: Lipopolysaccharide; NO: nitric oxide.

Declarations

DATA AVAILABILITY

The data used to support the findings of this study are available from the first author upon request.

COMPETING INTERESTS

The authors declare no competing financial interest.

AUTHOR CONTRIBUTIONS

Suya Ma wrote the manuscript. XW constructed the pharmacological networks. Jing Shi revised the manuscript. All authors were responsible for reviewing data. All authors read and approved the final manuscript.

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Figures

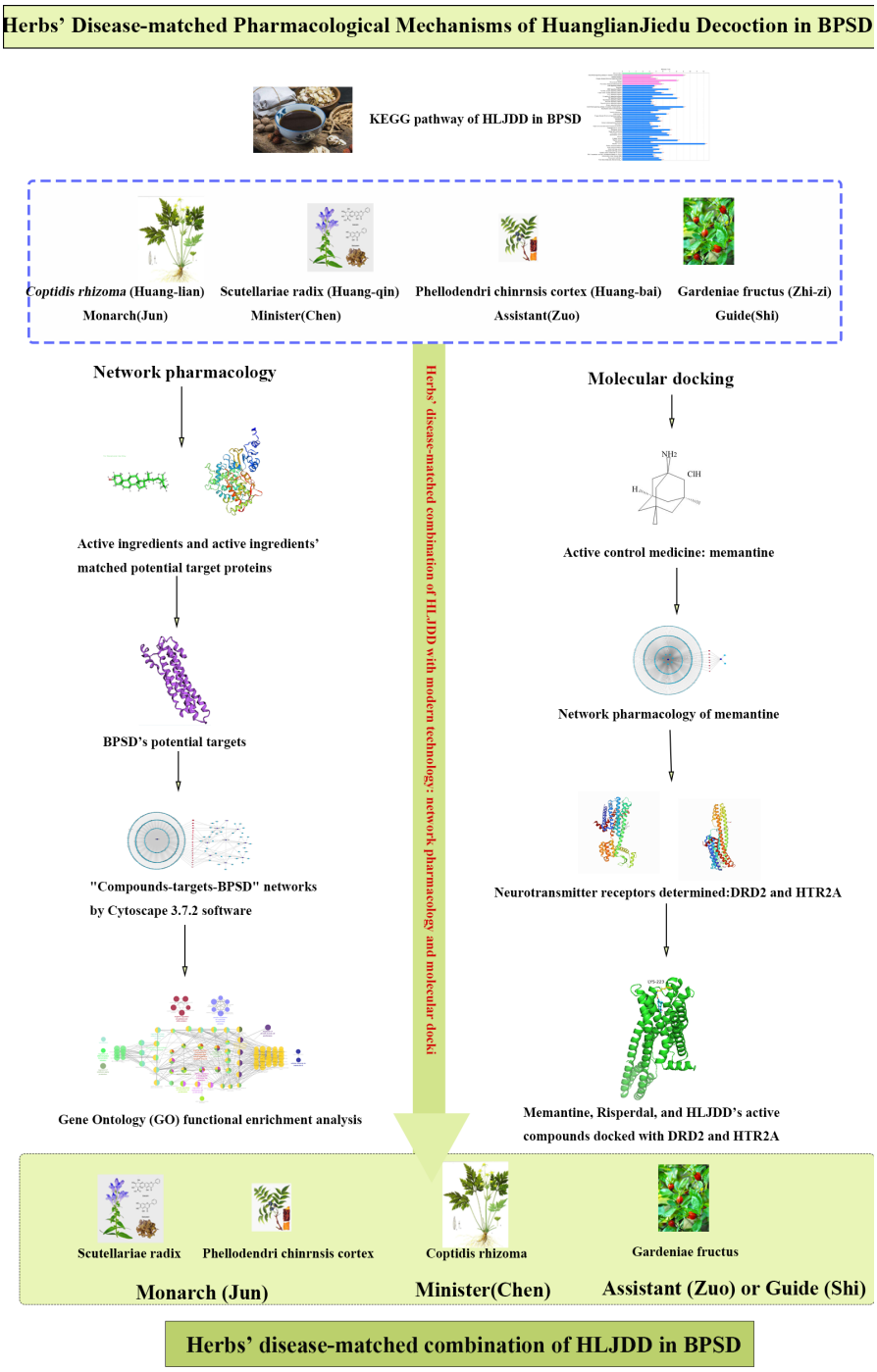

Figure 1

Schematic presentation of the method to discover the herbs' disease-matched combination of HLJDD in treating BPSD

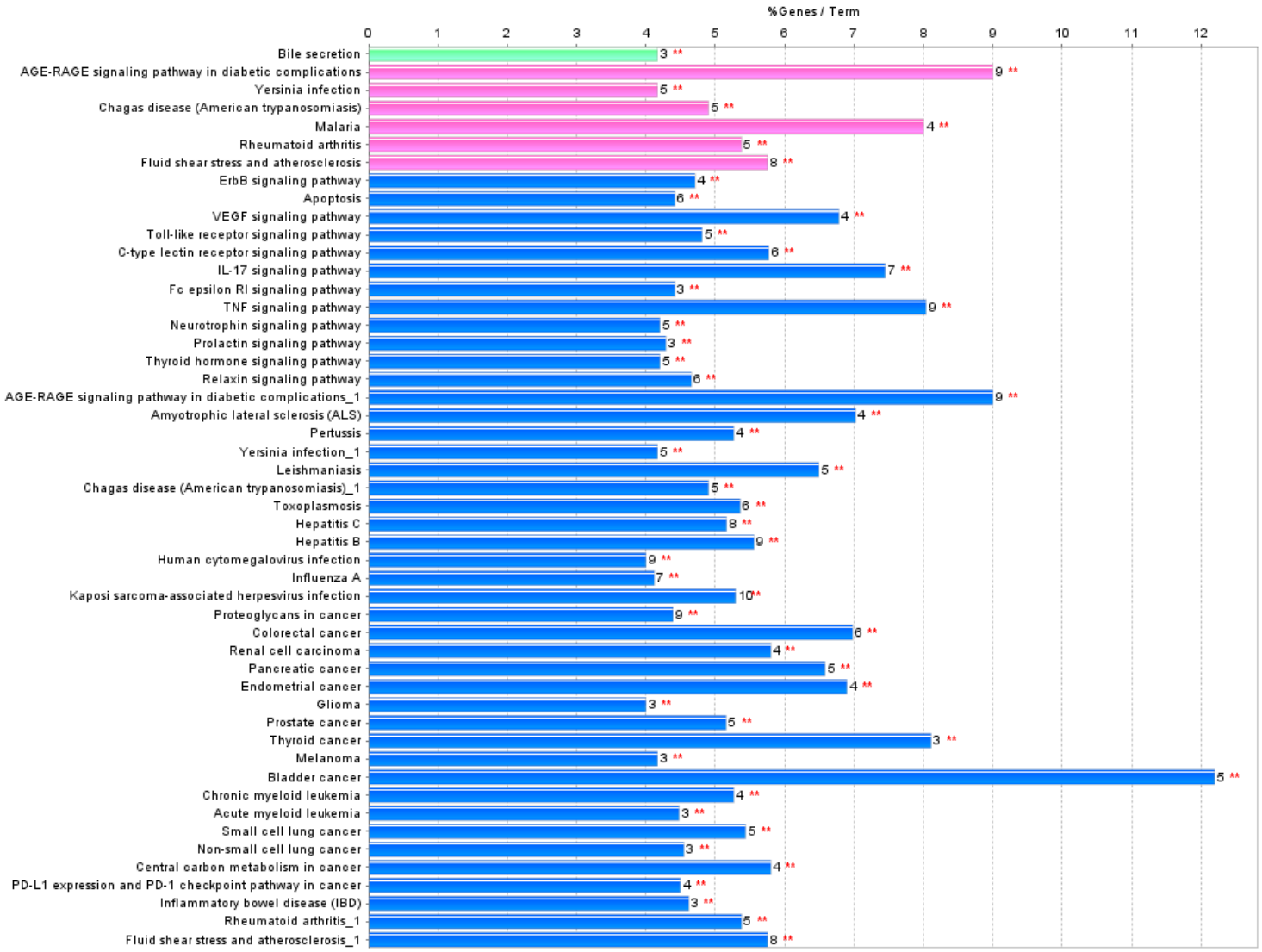

Figure 2

KEGG signaling pathway of HLJDD in treating BPSD.

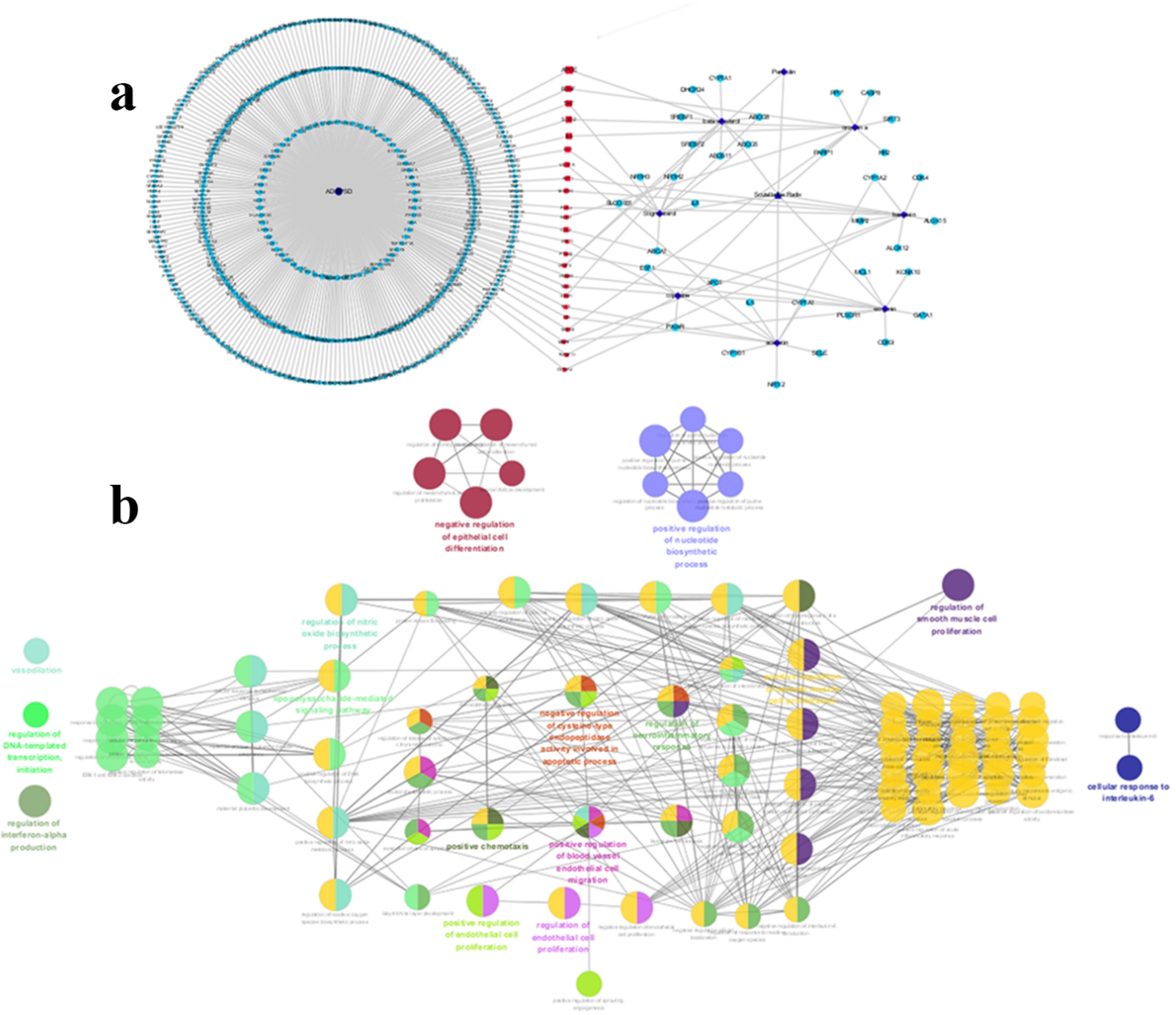

Figure 3

Schematic presentation of *Scutellariae radix*'s potential mechanism in treating BPSD. **a** The "compounds-targets-BPSD" network of *Scutellariae radix*. This systematic approach successfully revealed 24 key protein targets related to BPSD. **b** GO biological processes analysis of *Scutellariae radix*. *Scutellariae radix*'s key protein targets involved 156 biological processes, such as positive regulation of smooth muscle cell proliferation, lipopolysaccharide-mediated signaling pathway, and neuroinflammatory responses.

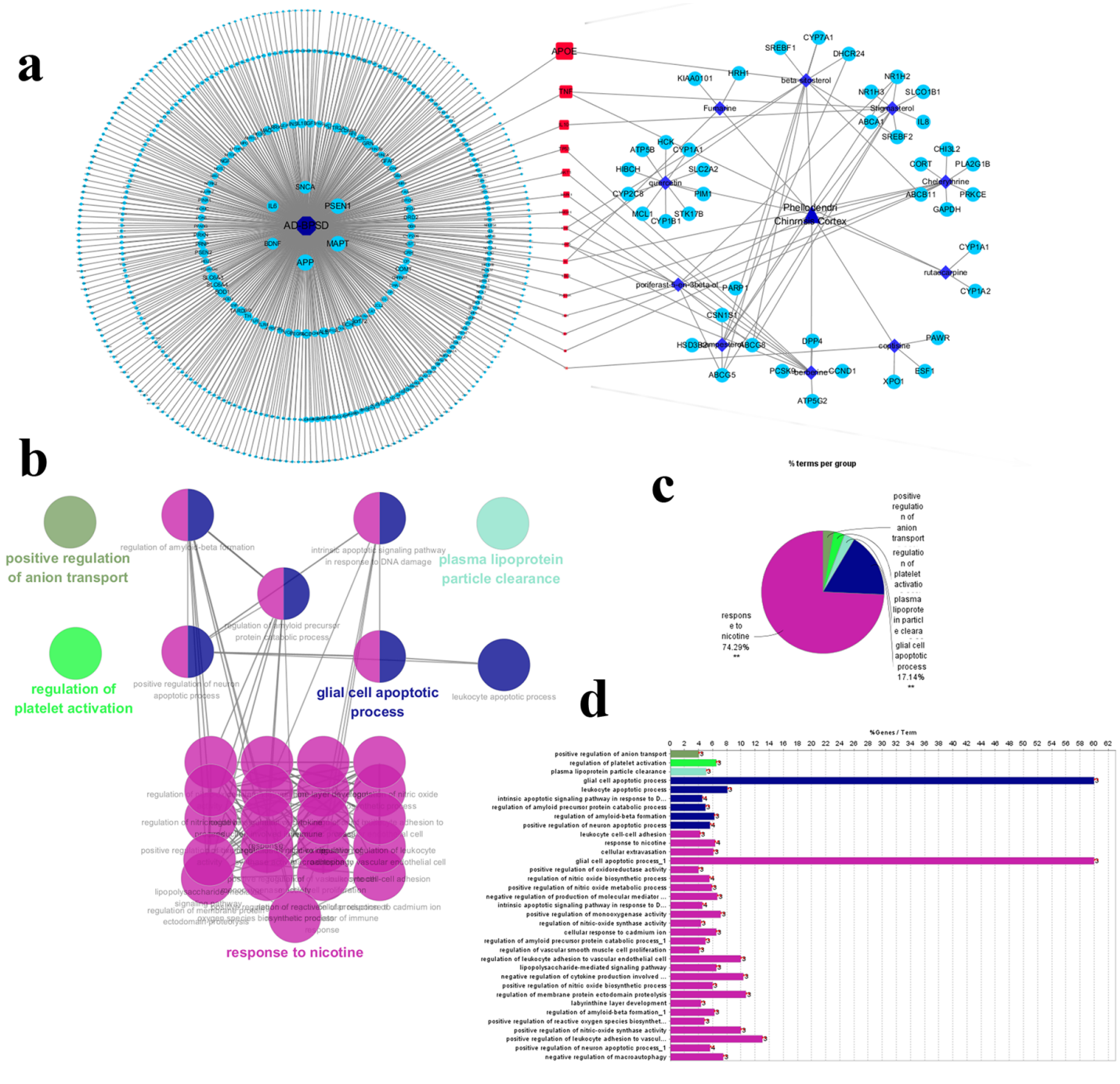

Figure 4

Schematic presentation of *Phellodendri chinrnsis cortex*'s potential mechanisms in BPSD. a The "compounds-targets-BPSD" network of *Phellodendri chinrnsis cortex*. Fifteen key protein targets were involved in BPSD. b, c, d GO biological process analysis of *Phellodendri chinrnsis cortex*. *Phellodendri chinrnsis cortex*'s key protein targets involved 35 biological processes including responses to nicotine, glial cell apoptotic processes, and positive regulation of anion transport.

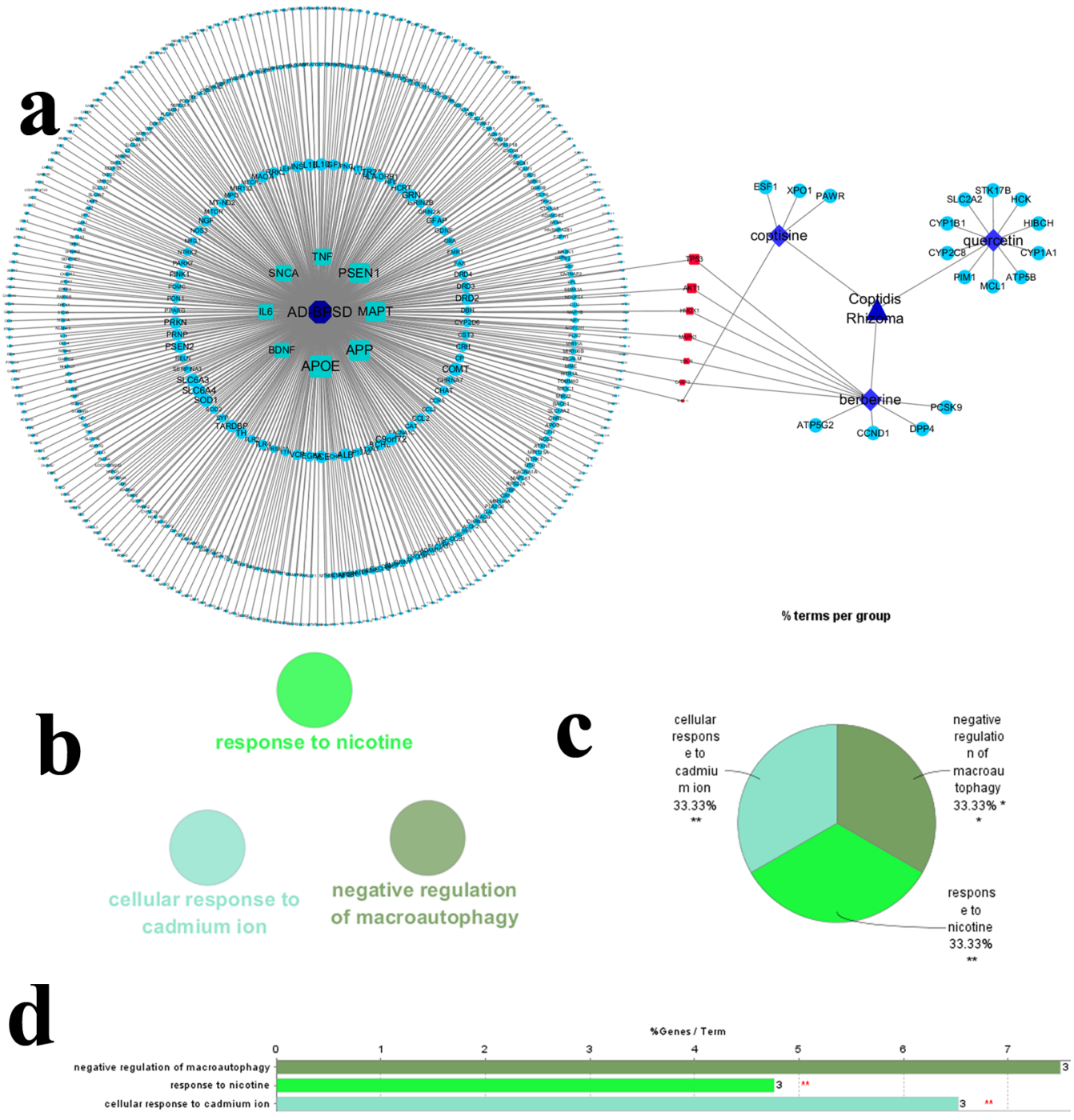

Figure 5

Schematic presentation of *Coptidis rhizoma*'s potential mechanisms in treating BPSD. a The "compounds-targets-BPSD" network of *Coptidis rhizoma*. Seven key protein targets were associated with BPSD. b, c, d GO biological processes analysis of *Coptidis rhizoma*. The key protein targets of *Coptidis rhizoma* are involved in three biological processes; negative regulation of macroautophagy, responses to nicotine, and cellular responses to cadmium ions.

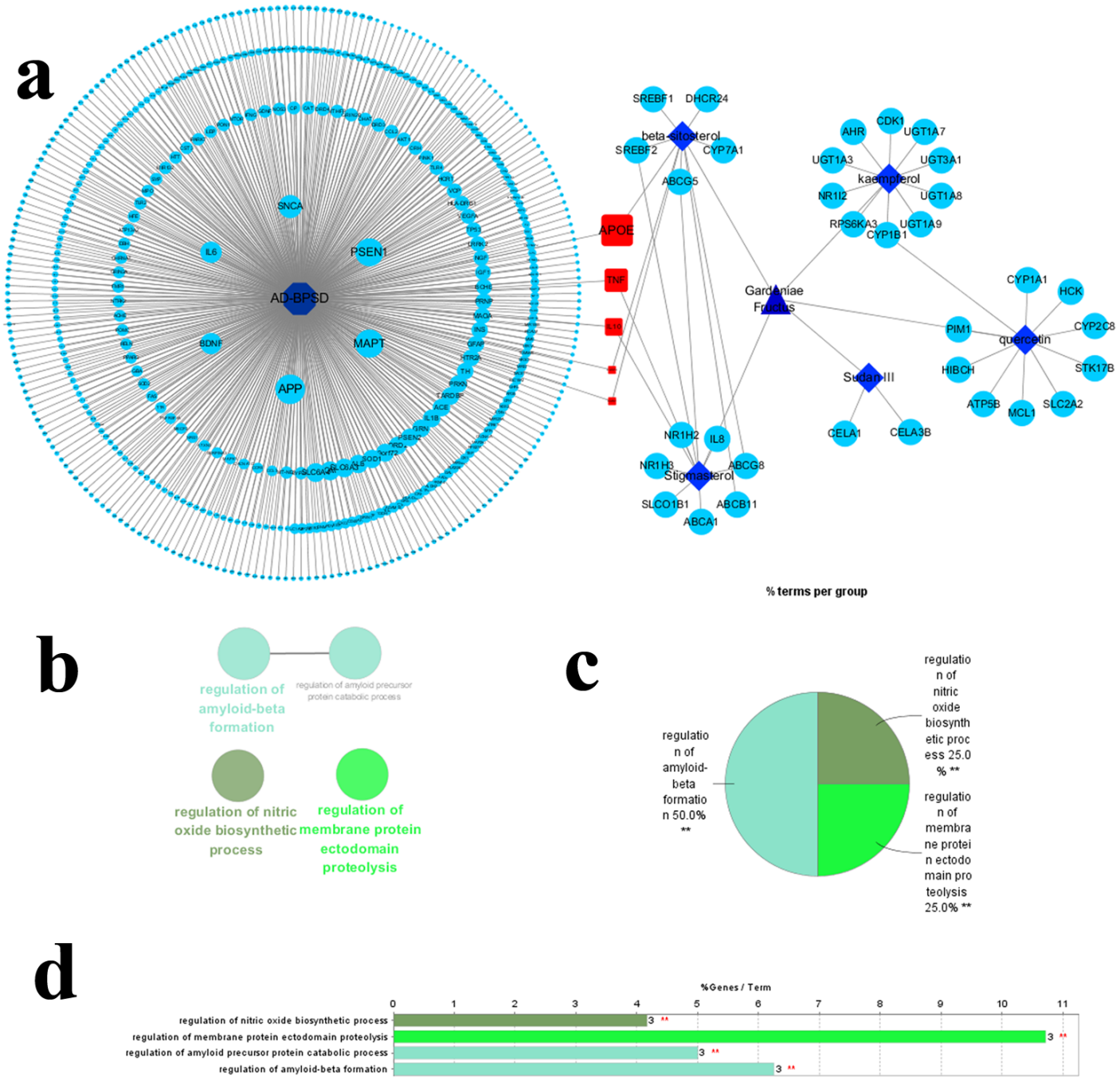

Figure 6

Schematic presentation of *Gardeniae fructus*'s potential mechanisms in BPSD. a The "compounds-targets-BPSD" *Gardeniae fructus* network. Five key protein targets were identified. b, c, d GO biological processes analysis of *Gardeniae fructus*. *Gardeniae fructus*'s key protein targets are involved in 4 biological processes; regulation of amyloid precursor protein catabolic processes, regulation of membrane protein ectodomain proteolysis, regulation of nitric oxide biosynthetic processes, and regulation of amyloid-beta formation.

Figure 7

Schematic 3D presentation of the molecular docking model with DRD2 and HTR2A